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Dual Antiplatelet Therapy (DAPT) in Coronary Artery Disease: A Daunting Dilemma

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Abstract: Percutaneous coronary intervention(PCI) with stenting for the treatment of acute coronary syndrome(ACS) is the contemporary standard of care. Such treatment is followed by Dual anti-platelet therapy(DAPT) comprising of aspirin and a P2Y12 inhibitor. The efficacy of this therapy has been well established but the optimal duration of DAPT remains elusive, and has thus far attracted a prodigious deal of scientific attention. Decision regarding DAPT duration can be challenging clinically in the modern era with the evolution of newer stents, more potent antiplatelet agents and novel anticoagulant drugs in addition to an older patient population with multiple comorbidities. Major societal guidelines have emphasized comprehensive assessment of ischemic and bleeding risk, in turn recommending individualization of DAPT duration, thus encouraging "shared decision making". The following review is aimed at critically evaluating the available evidence to help make these crucial clinical decisions regarding duration of DAPT and triple therapy.

Keywords: dual anti platelet therapy; acute coronary syndrome; stents

1. Introduction:

Coronary revascularization with percutaneous intervention(PCI) is currently the standard of care in the treatment of patients with acute coronary syndrome(ACS), and has become one of the most frequently performed therapeutic procedures in Medicine[1]. Dual anti-platelet therapy (DAPT) comprising of aspirin and a P2Y12 inhibitor is one of the most commonly prescribed therapies in cardiovascular medicine. The optimal duration of DAPT after stent implantation has been a matter of intense debate and has attracted a great deal of scientific attention. As we celebrate the various advances in the techniques and technology of transcatheter therapeutics in this 40th year of Interventional Cardiology, optimal duration of DAPT continue to be elusive. Most recent transatlantic guidelines have called for the comprehensive assessment of ischemic and bleeding risks thus emphasizing individualization of DAPT[2,3]. The following review is aimed at critically evaluating the available evidence to help make crucial clinical decisions regarding duration of DAPT and triple therapy.

2. Evolution of PCI:

Careful examination of the history of PCI provides important insights into the evolution of DAPT[4]. Initial enthusiasm of angioplasty as an alternative to bypass surgery was stifled by the limitations owing to abrupt vessel closure due to recoil, dissections and restenosis thus leading to development of stents to offer luminal integrity without compromising safety[5,6]. Bare metal stents(BMS) were affected by restenosis with a need for repeat revascularization in up to one third of the patients[7] besides lethal early stent thrombosis (EST; <30days)[8] . Drug eluting stents (DES) were designed and in their first iteration, they were clearly superior to BMS in reducing restenosis and rates of repeat revascularizations[9–12].There was a trend for increased late stent thrombosis(LST) (>30days <1 year) and very late stent thrombosis (VLST) (>1 year), and this was felt to be multifactorial. Subsequently, second generation DES endowed with better biocompatibility, thinner platforms ensured improved vessel healing[13]. In a meta-analysis of four randomized controlled trials(RCTs) comparing Everolimus eluting stents (second generation DES) vs Paclitaxel eluting stents (first generation DES) a significant reduction in stent thrombosis (ST) was noted (0.7% vs 2.3%; odds ratio[OR]: 0.32; p<0.00001)[14]. To modify the interference with vasoregulation, chronic inflammation, neoatherosclerosis and device fractures, in turn leading to target-lesion failure(TLF)[15,16] bioresorbable vascular scaffolds(BVS)[16–18] were introduced. However, there is a lot to desire with the current BVS technology and the most recent recommendations dissuade providers from their preferential use over DES[19]. Till good quality evidence emerges from RCTs against contemporary DES powered for a surrogate end point of clinical efficacy, BVS is unlikely to be in routine use.

3. Rationale for DAPT:

The idea of antiplatelet therapy in reducing thrombosis following PCI was kindled three decades ago[20]. However, use of DAPT became a standard in BMS era to reduce the rates of EST[21]. DAPT was reserved for 3-6 months for the use of first generation DES to prevent ST and to ensure endothelialization. The DAPT duration in the earlier times of first generation DES era was up to 6 months[9,10,22]. With the realization of higher thrombotic milieu in the first year with these stents, especially with interruption of DAPT[23,24], consensus based guidelines recommended prolonging DAPT to up to 12 months[25]. This philosophy was reinforced by the observed benefits of such therapy in prevention of atherothrombosis of non-stented segments in coronary vasculature[26]. With the ubiquitous use of second generation DES with lower rates of ST, and evidence from multiple RCTs supporting shorter DAPT, guidelines proposed optimal DAPT duration of 6-12 months[2,27]. Subsequently, two large RCTs demonstrated benefit in stent related and unrelated ischemic events at the cost of increased bleeding[28,29] thus re-igniting the short vs long debate. The most recent iteration of guidelines takes cognizance of all these data and call for shared decision making and individualizing DAPT[30].

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4. Antiplatelet agents and their landmark trials:

Table1 enumerates the cardinal pharmacological properties of various P2Y12 inhibitors which are an essential component of DAPT. Importantly, the differences in the recommended periods of discontinuation of these agents in the lead up to non-emergent surgery should be noted.

TABLE 1 Comparative properties involving oral P2Y12 inhibitors

N/A= not applicable

- In patients with ACS previously exposed to clopidogrel, switching to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindicated (IB)[30]
- All other switching between P2Y12 inhibitors may be considered in cases of side effects/intolerance(IIb-C)[30]

While an exhaustive review of all the trials is beyond the scope of this review, ***Table 2*** summarizes the evidence leading to the inception of various antiplatelet agents in the treatment of coronary artery disease (CAD). The outcome measures observed in these trials highlight the ability of these drugs in improving cardiovascular outcomes, albeit at the cost of increasing bleeding.

TABLE 2 Landmark trials of antiplatelet agents

MACCE= major adverse cardiovascular and cerebrovascular events; **ICH**= Intracranial hemorrhage

ISIS-2[31] = Second **I**nternational **S**tudy of **I**nfarct **S**urvival Collaborative Group; **CAPRIE**[32]= A randomized, blinded, trial of **C**lopidogrel versus **A**spirin in **P**atients at **R**isk of **I**schemic **E**vents; **CURE**[33]= **C**lopidogrel in **U**nstable angina to prevent **R**ecurrent **E**vents; **PCI-CURE**[34]= Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention; **CREDO**[35]= The **C**lopidogrel for the **R**eduction of **E**vents **D**uring **O**bservation; **TRITON-TIMI 38**[36]= **TR**ial to assess **I**mprovement in **T**herapeutic **O**utcomes by optimizing platelet Inhibitio**n** with Prasugrel–**T**hrombolysis **i**n **M**yocardial **I**nfarction, **PLATO**[37]= **Pl**atelet inhibition **A**nd pat**i**ent **O**utcomes; **TRILOGY ACS**[38]= The **TaRg**eted platelet **I**nhibition to c**L**arify the **O**ptimal strate**G**y to medicall**Y** manage **A**cute **C**oronary **S**yndromes; **CHAMPION PHOENIX**[39]= Effect of platelet inhibition with cangrelor during PCI on ischemic events; **TRACER**[40]= **T**hrombin-**R**eceptor **A**ntagonist for **C**linical **E**vent **R**eduction.

The benefits of DAPT in a RCT setting were first seen in the ***CURE***[33] trial in which combination of aspirin and clopidogrel in comparison with aspirin monotherapy was assessed in patients undergoing PCI in myocardial infarction(MI) without ST elevation. 12,562 patients were enrolled and at mean follow up of 9 months, DAPT was associated with a significant reduction in the composite primary end point of cardiovascular mortality (CVM), non-fatal MI, or stroke [9.3% vs. 11.4%, Relative risk(RR):0.80; p<0.001; Number needed to treat(NNT)= 48]. However, this came at a cost of increased rate of major bleeding [3.7% vs. 2.7%, RR: 1.38; p=0.001]. This trial was instrumental in establishing the 12 months of DAPT as standard of care in the treatment of ACS patients.

In ***TRITON-TIMI 38***[36] trial, 13,608 patients with ACS awaiting PCI were randomized to either prasugrel or clopidogrel in addition to the usual care. At mean follow-up of 14.5 months, composite primary end point of CVM, non-fatal MI, or stroke was significantly lower in the prasugrel group [9.9% vs. 12.1% (HR:0.81; p<0.001; NNT=46]. These benefits came at the cost of increased risk of bleeding. Major bleeding was higher with the use of prasugrel group vs. clopidogrel (2.4% vs. 1.8%, HR 1.32; p=0.03). Also, greater in the prasugrel group

was the rate of life-threatening bleeding (1.4% vs. 0.9%; p=0.01), including nonfatal bleeding (1.1% vs. 0.9%; HR 1.25; p=0.23) and fatal bleeding (0.4% vs. 0.1%; P=0.002). There was no significant difference in either CVM or all-cause mortality (ACM). Interestingly, the benefits appeared within days from randomization and persisted beyond the first year. In the sub-group analysis of patients with ST elevation MI(STEMI), there was an even greater benefit in the primary outcome (6.5% vs. 9.5%; HR: 0.68; p= 0.0017) without the incremental bleeding risk[41]. In the subsequent ***TRILOGY ACS*** trial[38], there was no significant risk reduction of primary endpoint with the use of prasugrel in patients with unstable angina(UA) and non-ST elevation myocardial infarction(NSTEMI) treated without revascularization.

In one of the largest RCTs', Ticagrelor was compared to clopidogrel in the ***PLATO*** trial[37]. PLATO randomized 18,624 patients with ACS (37.5% presenting with STEMI) were randomized to ticagrelor or clopidogrel in addition to standard care. At 12months, ticagrelor group had lower composite primary outcome of CVM, MI, or stroke (9.8% vs. 11.7%; HR: 0.77-0.92; p<0.001) and there was insignificant increase in major bleeding (11.6% vs. 11.2%; HR: 1.04; p=0.43). A reduction in vascular mortality (4% vs. 5.1%; HR: 0.79; p<0.001) and ACM (4.5% vs. 5.9%; HR: 0.78; p<0.001) were also noted. However, the reduction in stroke was statistically not significant (1.5% vs. 1.3%; HR: 1.17; p=0.22). Ticagrelor is the only antiplatelet agent shown to decrease the ACM compared to clopidogrel though given the hierarchical statistical design of this study, the significance of this finding is attenuated.

The real life experience of ticagrelor was evaluated in ***SWEDEHEART*** registry[42]. This non-randomized prospective cohort study of 45,073 ACS patients in Sweden demonstrated amplified benefits of ticagrelor in comparison with clopidogrel. The composite primary outcome of ACM, re-admission with myocardial infarction (MI) or stroke was lower with ticagrelor group [11.7 vs. 22.3%, adjusted HR 0.85]. In a subset of patients undergoing PCI on ticagrelor, the PCI-related in-hospital bleeding was higher [3.7 vs. 2.7%, adjusted OR: 1.57 (1.30-1.90)]. This registry data certainly corroborates the evidence from PLATO trial but some major differences are noteworthy, as evidenced by the mean age of patients in the present study being 8 years higher (70 vs. 62 years) and a higher proportion of patients with history of stroke (10.8% vs. 3.9%) and heart failure (10.3% vs. 5.6%).

5. Duration of DAPT:

Traditionally 12 months of DAPT duration has been considered as the standard with 3months and 6 months of DAPT representing short DAPT (S-DAPT) and > 12 months representing longer DAPT (L-DAPT) durations. The conception of S-DAPT was to reduce bleeding without compromising the safety and efficacy of PCI, while L-DAPT was tested with a hope to improve stent related and stent unrelated ischemic (Atherothormbotic) events. With the development of better stent platforms amounting to reduction in rates of ST and restenosis paralleled by development of potent antiplatelet agents, the "optimal" duration of DAPT has been extensively evaluated but still remains elusive. This constant dualistic debate of "short" vs "long" has certainly lead to significant uncertainty and confusion among the treating providers. Some observers have recommended an end to such a dogmatic approach laced with academic debates, and emphasized shared decision making and individualization of therapy[43].

5.1 EVIDENCE ON DAPT DURATION

Till date there have been several RCTs' and several meta-analyses of these trials to evaluate for optimal duration of DAPT. At the outset, it is crucial to note the several limitations to these trials including but not limited to flaws in design ultimately leading to lack of power in detecting difference in hard endpoints, varying patient and lesion complexity, diverse clinical settings, low event rates, different times of randomization, slow

enrollment, dissimilar endpoints, differential use of stents (BMS; first vs second generation DES) thus making comparable interpretation difficult and yielding inconsistent results[44].

5.2a RCT with S-DAPT

There have been 12 RCTs' using S-DAPT to determine its relative efficacy in preventing major adverse cardiovascular and cerebrovascular events (MACCE) including ST, and to determine the relative safety of such DAPT duration for major bleeding in comparison with standard or L-DAPT. Unfortunately, none of these trials were independently powered to evaluate the rates of safety end point of ST which is infrequent.

5.2b S-DAPT vs. standard DAPT duration

The hypothesis of non-inferiority of S-DAPT to standard care was tested in 9 RCTs. These are comparatively summarized in ***Table 3***.

TABLE 3 Comparative features of randomized controlled trials(RCTs) for short DAPT(S-DAPT) Vs. standard DAPT

ACS= acute coronary syndrome; **DM**= diabetes mellitus; **1G**= first generation; **2G**= second generation; **MI**= myocardial infarction; **TVR**= target vessel revascularization; **p_{ni}**= p value for non-inferiority; **ST**= stent thrombosis; **TIMI**= thrombolysis in myocardial infarction; **BARC**= bleeding academic research consortium; **TLR**= target lesion revascularization

EXCELLENT[45]**=** Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the **E**fficacy of **X**ience/Promus versus **C**ypher to R**E**duce **L**ate **L**oss After St**ent**ing randomized, multicenter study; **RESET**[46]= **RE**al **S**afety and **E**fficacy of 3-month dual antiplatelet **T**herapy following Endeavor zotarolimus-eluting stent implantation; **OPTIMIZE**[47]= Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents; **SECURITY**[48]= Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy; **ISAR-SAFE**[49]= **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **Safe**ty and Efficacy of 6 months' DAPT after DES; **I LOVE IT**[50]= a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting; **IVUS XPL**[51]= 6-Month Versus 12-Month Dual-Antiplatelet Therapy Following Long Everolimus-Eluting Stent Implantation; **DAPT-STEMI**[52]= A prospective, randomized, open-label trial of 6-month versus 12-month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction; **REDUCE**[53]= Randomized evaluation of short-term dual antiplatelet therapy in patients with acute coronary syndrome treated with the COMBO dual therapy stent

It is imperative to note that, patients were randomized to DAPT duration at the time of stent implantation in all trials except in ISAR-SAFE[49]. There is significant heterogeneity among these trials with regards to the enrollment of patients with ACS, diabetes, and the type of stent used.

The ***ISAR-SAFE***[49] trial was actually designed to enroll 6000 patients with a non-inferiority hypothesis. However, it was prematurely terminated after enrolling 4000 patients' due to slow enrollment but still achieved non-inferiority. These patients who had undergone PCI with DES were randomized at 6 months to interrupt or continue 12 months of DAPT. There was a fair representation of patients with ACS (40%), with 10% suffering from STEMI and 30% with multivessel CAD. Second generation DES were predominantly used (89%) and mostly used in treatment of single lesion (63%). Primary composite outcome of death, MI, ST, stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding occurred in 1.5% of patients on S-DAPT and 1.6% with standard DAPT (p_{ni}<0.001 with predefined noninferiority margin of 2%). Both groups had similar rates of TIMI major bleeding.

Two trials with a novel approach were presented at Transcatheter Cardiovascular Therapeutics meeting (TCT 2017), Denver, CO, November 1, 2017. In the ***DAPT-STEMI*** trial, patients with STEMI and undergoing primary

PCI with a second-generation DES (zotarolimus-eluting stent [ZES]) were randomized in a 1:1 fashion to receive either 6 months (n = 433) or 12 months of DAPT (n = 437) to assess the safety and efficacy of such DAPT durations. Importantly, patients without any events in the first 6 months [MI, ST, target vessel failure (TVF) or target lesion failure (TLF), or stroke/bleeding requiring DAPT discontinuation] were included in the analysis. Patients requiring left main coronary artery (LMCA) intervention were excluded. All three contemporary P2Y12 agents were used (clopidogrel: 42%, prasugrel: 30%, ticagrelor: 29%).The primary outcome, ACM, MI, revascularization, stroke, and TIMI major bleeding at 18 months was lower in 6-month vs. 12-month DAPT (4.8% vs. 6.6%, p_{ni} = 0.004). Although, this 2-year outcome data establishes non-inferiority of S-DAPT in STEMI patients, this trial was not powered to evaluate for individual safety end points. Long-term data would be crucial before such short DAPT duration is adapted into clinical practice in the treatment of ACS.

In the ***REDUCE*** trial, 3-Month vs. 12-Month DAPT was assessed for safety and efficacy after implantation of a bioabsorbable polymer-based metallic sirolimus eluting stent with a luminal CD34+ antibody coating in patients with ACS. The rationale behind testing such a stent was to use the combination of abluminal release of sirolimus (to prevent neointima formation), and capture of endothelial progenitor cells (to enhance stent re-endothelialization). The cumulative survival free from the primary study end-point of ACM, MI, ST, stroke, TVR, or bleeding for 3-month vs. 12-month DAPT, was 91.7% vs. 91.5%, p_{ni} < 0.001. There were, however, concerning safety signals with a higher risk of ACM (1.9% vs. 0.8%, p=0.07) and ST (1.2% vs. 0.4% p=0.08), with shorter duration of DAPT with no difference in bleeding. Cautious interpretation of these results suggests that though the noninferiority hypothesis was met, the margin of noninferiority was quite generous, and the trend of some ischemic endpoints impoverished the 3-month DAPT group.

5.2c S-DAPT vs L-DAPT

Three RCT till date have been published as summarized in ***Table 4***.

TABLE 4 Comparative features of randomized controlled trials(RCTs) for short DAPT(S-DAPT) Vs. long DAPT(L-DAPT)

ACS= acute coronary syndrome; **DM**= diabetes mellitus; **1G**= first generation; **2G**= second generation; **MI**= myocardial infarction; **TVR**= target vessel revascularization; **p_{ni}**= p value for non-inferiority

PRODIGY[54]**=** The **PRO**longing **D**ual Ant**I**platelet Treatment After **G**rading Stent-Induced Intimal H**y**perplasia Study; Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial; **ITALIC**[55]= **I**s **T**here **A** **L**ife for DES after DI**S**continuation of **C**lopidogrel, 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin; **NIPPON**[56]= Dual Antiplatelet Therapy for 6 Versus 18 Months After Biodegradable Polymer Drug-Eluting Stent Implantation

The implications of the data from these trials is certainly influenced by the heterogeneity of patients and of the stents used. These trials were powered to look for difference in bleeding, and due to the low ischemic event rates, any conclusions drawn to qualify the efficacy would be inaccurate. More recently, ***NIPPON*** trial[56] was performed in Japan using bioabsorbable polymer-based DES. This trial tested for non-inferiority of 6-month DAPT vs. 18month DAPT, and randomized 3775 patients. The composite primary outcome of ACM, MI, stroke, and major bleeding was similar (1.92% vs 1.45%) thus meeting the non-inferiority. However, the margin for such non-inferiority was set wide at 2% which exceeded the event rate of the experimental arm and the study was prematurely terminated thus raising concerns and these results should be judiciously interpreted.

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5.2d Standard DAPT vs L-DAPT

The hypothesis of superiority of L-DAPT in reducing the VLST and other ischemic events in comparison with standard DAPT was tested in four RCTs'. These are comparatively represented in ***Table 5***. In all these trials, event-free patients on 1 year of DAPT were randomized to single antiplatelet therapy (SAPT) vs continuation of DAPT with clopidogrel or prasugrel for varying periods of time.

TABLE 5 Comparative features of randomized controlled trials(RCTs) for standard DAPT Vs. long DAPT(L-DAPT)

ACS= acute coronary syndrome; **DM**= diabetes mellitus; **1G**= first generation; **2G**= second generation; **MI**= myocardial infarction; **TVR**= target vessel revascularization; $\mathbf{p_{ni}}$= p value for non-inferiority; **ST**= stent thrombosis; **MACCE**= major adverse cardiovascular and cerebrovascular events; ISTH= international society of thrombosis and hemostasis

DAPT[28]= **D**ual **A**nti**P**latelet **T**herapy study, Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents; **DES LATE**[57]= Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation; **ARCTIC INTERRUPTION**[58]= Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation; **OPTIDUAL**[59]= Stopping or continuing clopidogrel 12 months after drug-eluting stent placement

DAPT[28] trial deserves a special mention for being the only trial which was adequately powered for safety and efficacy endpoints, and also providing some significant insights into L-DAPT. In this trial, 9961 patients who were event free after 12 months' of DAPT and compliant to DAPT were randomized to continue DAPT for 30 months' vs SAPT (with aspirin). About 26% of the participants had ACS and importantly, 47% of the patients received Everolimus eluting stents (EES) and only clopidogrel (65%) and prasugrel (35%) were used as a part of DAPT. In the DAPT group, there was 1% lower VLST and 1.6% fewer MACCE events driven by 2% reduction in rates of MI. These benefits came at a cost of 0.9% absolute increase in moderate to severe **GUSTO** (**G**lobal **U**tilization of **S**treptokinase and **t**-PA for **O**ccluded Coronary Arteries) bleeding and 2.6% increase in **BARC** (**B**leeding **A**cademic **R**esearch **C**onsortium) 2, 3, or 5 bleeding. At 33 months' follow-up, ACM was higher in the DAPT group (2% vs 1.5%, p=0.052). This increase was attributable to bleeding, trauma, and cancer[60].The authors also interpreted this finding as being due to chance and later it was noted that at baseline, a greater number of patients with a prior history of cancer had been randomly allocated to extended DAPT duration group thus explaining 7 of the 26 deaths in that group. Food and drug administration(FDA) passed a revision refuting an association of increased mortality with extended use of clopidogrel[61]. However, such an increase in fatalities were also observed in other studies[62] with other agents.

More recently, the hypothesis of 48 months of DAPT with clopidogrel being superior to 12 months of DAPT was tested in ***OPTIDUAL***[59]. The enrollment was prematurely stopped in this trial. Superiority of L-DAPT could not be established as the composite primary end-point of death, MI, stroke, or major hemorrhage were similar in both the arms (5.8% vs. 7.5%; HR 0.75; p=0.17). Safety end-point of moderate and severe GUSTO bleeding (1.9% vs. 1.7%) and BARC 2, 3, or 5 bleeding (2.6% vs. 2.9%) were similar in both groups.

5.2 e Other RCTs with DAPT duration

Three other RCTs are worthy of review as they deal with safety and efficacy of DAPT in varied clinical settings.

In ***CHARISMA***[63] (**C**lopidogrel for **H**igh **A**therothrombotic **R**isk and **I**schemic **S**tabilization, **M**anagement, and **A**voidance) trial, 15,603 patients with cardiovascular risk factors or a history of vascular disease were randomized to receive DAPT with aspirin and clopidogrel vs SAPT with aspirin. The composite primary

endpoint of MACCE at 28 months was similar in both groups (6.8% vs 7.3%, p=0.22), and there was no significant difference in major bleeding. However, there was 1% risk reduction of MACCE in DAPT group vs SAPT (6.9% vs 7.9%; RR 0.88; p=0.046) when analyzed in the pre-specified group of patients with established cardiovascular disease[64]. Patients with prior MI, stroke, or symptomatic peripheral arterial disease (PAD) derived significant benefit from DAPT (7.3% versus 8.8% HR: 0.83, p = 0.01) and there was no significant difference in the rate of severe bleeding (1.7% vs. 1.5%, HR: 1.12; p = 0.50); moderate bleeding was significantly increased (2.0% vs.1.3%, HR:1.60; p = 0.004)[64].

In ***PEGASUS-TIMI 54***[29] (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54) trial; 21,162 patients with a prior history of MI in preceding 1-3 years, were randomized in a double blinded regimen in 1:1:1 into three groups. This trial was designed to test the efficacy of DAPT (Ticagrelor 90mg twice daily or 60 mg twice daily) with aspirin vs SAPT with aspirin. There was 1.2-1.3% absolute risk reduction (ARR) of MACCE events in DAPT groups' vs SAPT at the cost of 1.2-1.5% increase in major bleeding. However, there was no excess in fatal bleeding or intracranial hemorrhage. Sub-group analysis of higher risk patients demonstrated more robust benefits. In the diabetic sub-group, there was an ARR of 1.5% (p=0.03)[65]. Patients with prior vascular disease demonstrated a higher event rate, and despite an increased bleeding risk, there was a nearly 5% ARR[29] of ischemic events. Patients with renal disease also had higher event rate but drew more benefit from DAPT therapy with ARR 2.7%[66] of ischemic events.

These two trials underpin the ischemic benefit derived from L-DAPT especially in higher risk patients, albeit at the cost of increased bleeding risk. However, it is noteworthy that a majority of these patients had a period of interruption in DAPT after their initial ischemic event. In fact, in PEGASUS pre-specified subgroup analysis, patients with discontinuation period of 1 year or longer before re-initiation of DAPT did not derive any benefit[67].

In the recently published ***SENIOR*** *trial*,[68] 1200 elderly patients (≥75 years of age) with CAD, were randomly assigned to DES or BMS after an intended duration of DAPT (1 month for stable CAD, 6 months for ACS). There was significant reduction in primary composite endpoint of ACM, MI, stroke, ischemia driven target lesion revascularization in DES vs BMS [16.4% vs 11.6%, p=0.016; RR 0.71] thus yielding NNT=21. This difference was mainly driven by ischemia driven target lesion revascularization (1.7% vs. 5.9%, p=0.0002). Net clinical benefit encompassing MACCE and BARC 2-5 bleeding was significantly lower in DES vs BMS [14.4% vs. 19.2%, p=0.0239; RR 0.75]. Interestingly, ST was low and not different between the groups (0.5% vs 1.4%, p=0.12). It has to be noted that the aim of this study was to compare the type of stents but not the DAPT duration. However, it provides valuable information in this group that has not been well represented in prior RCTs'.

5.2 f Meta-analyses

The idea of net clinical benefit for the individual patient becomes complicated due the fact that these trials demonstrate reduced ischemic events and increased bleeding with prolongation of DAPT, although with a possible interaction with stent type. This generated a need for meta-analysis of these RCTs'. Many meta-analyses have been performed till date and they have differed significantly in the number of RCTs' included and also their designs[69–74].
In the largest meta-analysis till date[71] including 14 RCTs' involving 69,644 patients with ACM as the only primary endpoint, there was no significant difference in mortality with L-DAPT in comparison with S-DAPT (HR=1.05, 95% credible interval, 0.96-1.19). However, since this analysis included mixed populations, moderate heterogeneity was present (I^2=27%) for the treatment effects. In a recent meta-analysis[75] of five RCTs' with mean follow up of 2 years or longer involving 20,000 patients, S-DAPT was compared to L-DAPT .

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The primary end point was ST and secondary endpoints were ACM, CVM, MI, TVR, TIMI major bleeding and stroke. Compared to L-DAPT, S-DAPT was associated with higher MI [OR 1.48]. There were no significant differences between groups in all other end points.

6. Current guidelines

The current transatlantic guidelines on DAPT usage are summarized in ***Table 6***

TABLE 6 GUIDELINE STATEMENTS ON DAPT USAGE

ESC=European society of cardiology focused update on dual antiplatelet therapy in coronary artery disease[30]
ACC/AHA= American College of Cardiology/ American Heart association guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease[2]

7. Individualization of therapy

Decisions regarding DAPT duration are complex and they epitomize the current era of "personalized medicine". The net clinical benefit should be the ultimate goal of this shared decision. DAPT trial offers a decent outlook into this aspect.

In evaluation of net clinical benefit in the DAPT study participants, NNT for benefit from ischemic events was 100 based on 1% ARR for ST; NNT= 50 based on ARR 2% for MI. The number needed to harm(NNH) was 111 based on 0.9% absolute risk of increase (ARI) in bleeding with L-DAPT thus favoring such a strategy[28]. However, when a similar exercise is carried out for the pre-specified patients with second generation DES; NNT=200 based on ARR 0.5% for ST; NNT=91 based on ARR 1.1% and NNH=83 based on ARI 1.2% due to bleeding thus disfavoring L-DAPT for prevention of MACCE rate and mortality[76].

Hence, it's imperative to evaluate the factors conferring ischemic and bleeding risks as listed in ***Figure 1***. Though use of DAPT in reducing ischemic events[29,34] is well known, it is crucial to recognize the increased risk of bleeding with such therapy[29,33] which ultimately has adverse prognostic implications[77] as well.

FIGURE 1 BALANCE BETWEEN ISCHEMIC AND BLEEDING RISKS[43,78]

ST= Stent thrombosis; ACS= Acute coronary syndrome; DM= Diabetes mellitus; CKD= Chronic kidney disease; PCI= percutaneous coronary intervention; NSAID= Non-steroidal anti-inflammatory drugs, DAPT= Dual anti platelet therapy

Risk calculators, as endorsed by the most recent guidelines can be an instrumental in making decisions regarding the duration of DAPT[30]. These are summarized in ***Table 7***

TABLE 7 COMPARATIVE FEATURES OF TOOLS FOR RISK ESTIMATION

DM= Diabetes mellitus; MI= Myocardial infarction; PCI= Percutaneous coronary intervention, ACS= Acute coronary syndrome; LVEF= Left ventricular ejection fraction

DAPT score was developed to aid clinicians and patients in the assessment of ischemic and bleeding risks. Since the tool was developed from DAPT study data, it can only be applied to patients completing 12 months DAPT uneventfully. This score was internally validated in DAPT study with moderate discrimination [C statistic,

0.70; 0.68] and calibrated for both ischemia and bleeding risks (goodness-of-fit p=0.81, p=0.34)[78]. This tool was externally validated in the ***PROTECT*** (**P**atient **R**elated **O**u**t**comes with **E**ndeavor versus **C**ypher s**t**enting) trial cohort[79].

PRECISE-DAPT (Predicting bleeding Complications In patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy) study group developed a tool from eight RCTs'. The predictive performance of this tool was assessed in the derivation cohort and validated in 8595 patients from the ***PLATO*** trial and 6172 patients from ***BernPCI*** registry. In comparison with PARIS bleeding score, this tool demonstrated good discrimination and net reclassification of patients[80].

These tools have not yet been tested prospectively in a RCT setting, and are by no means perfect or substitutive to clinical judgement[81].

8. **Triple therapy**

Triple therapy refers to the use of oral anticoagulant (OAC) and DAPT. CAD is a common comorbid condition in patients with atrial fibrillation (AF), and its prevalence was reported as 60-65% in Medicare beneficiaries[82]. Guidelines recommend assessment of stroke risk by CHA_2DS_2VASc score in patients with AF, and for scores≥ 1-2, oral anticoagulant(OAC) is recommended to mitigate risk of thromboembolism commonly manifested as stroke[82,83]. An estimated 5-10% patients undergoing PCI have concomitant AF with a need for OAC[84]. Other clinical situations requiring triple therapy is in patients needing PCI, and with indications for anticoagulation for conditions like deep vein thrombosis(DVT)/pulmonary embolism (PE), mechanical heart valve, left ventricular thrombosis etc. Such therapy comes at a cost of excessive bleeding risk[85]. With the inception of direct oral anticoagulants and potent P2Y12 inhibitors, clinical decisions on triple therapy remain controversial in the ability to optimize the balance between prevention of stroke and ST without unduly increasing bleeding risk.

The following **Table 8** summarizes the salient findings from most recent RCTs.

TABLE 8 EVIDENCE ON TRIPPLE THERAPY

BMS= Bare metal stent; DES= Drug eluting stent; TIMI= Thrombolyisis in myocardial infarction; HR= Hazard ratio, CI= Confidence interval; MI= Myocardial infarction; TVR= target vessel revascularization, BID= twice daily, AF= Atrial fibrillation

WOEST[86]**= W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing ; **PIONEER AF-PCI**[87]= Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI; **REDUAL-PCI**[88]= Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

In the ***WOEST trial***[86], the warfarin was evaluated and 70% patients had AF as the indication for OAC, while 25-30% had ACS at presentation. The results demonstrated the superiority of dual therapy with warfarin and clopidogrel vs. triple therapy on account of significant reduction in the primary outcome which was any bleeding within 1 year of PCI (19.5% vs. 44.4%; HR 0.36, p<0.001) as well as reduction in ACM (2.5% vs. 6.4%; p=0.027). The heterogeneity of patients with various indications for OAC is a limitation of this study.

Subsequently, with the introduction and prevalent use of direct oral anticoagulants, PIONEER AF-PCI[87] used rivaroxaban and REDUAL-PCI[88] used dabigatran to evaluate the safety and efficacy of triple therapy exclusively in AF patients undergoing PCI.

In the **PIONEER AF-PCI**[87], there was 1:1:1 randomization of patients to receive low-dose rivaroxaban (15 mg daily) + P2Y12 inhibitor for 12 months; very low dose rivaroxaban (2.5 mg twice daily) +DAPT for 1, 6, or 12 months or standard therapy with dose adjusted warfarin + DAPT for 1, 6, 12 months per guideline recommended DAPT duration based on the indication and stent type. There was less bleeding in the rivaroxaban groups vs. warfarin (17.4% vs. 26.7%, HR 0.61; p<0.001) without significant difference in MACCE. The rivaroxaban groups had lower re-hospitalization rates in comparison to warfarin [(34.1% vs. 41, 5%, HR: 0.77, p=0.05); (31.2% vs.41.5%, HR: 0.74, p= 0.01)]. This trial establishes supremacy of rivaroxaban over warfarin in reducing bleeding and re-hospitalizations but it was criticized for the use of 15 mg dose of rivaroxaban which is not approved for use in AF. It has to be emphasized that since the huge majority of the patients received clopidogrel (95%), this data cannot be extrapolated to the use of other newer and more potent P2Y12 inhibitors as a part of triple therapy regimens.

The results from ***REDUAL-PCI***[88] were presented at American Heart Association Annual Scientific Sessions (AHA 2017), Anaheim, CA, November 14, 2017. In this trial, AF patients undergoing PCI were randomized in 1:1:1 fashion to dual therapy with dabigatran at a dose of 110 mg (n = 981) vs. dual therapy with dabigatran at a dose of 150 mg (n = 763) vs. triple therapy with warfarin (n = 981). In the dual therapy group, participants received clopidogrel or ticagrelor in addition to one of two doses of dabigatran. In the triple therapy group, participants received aspirin plus clopidogrel or ticagrelor in addition to warfarin. The duration of aspirin was 1 month after a BMS and 3 months after a DES. About 52% patients had ACS, 82% received DES and 10% received ticagrelor as the P2Y12 inhibitor. The primary safety outcome, incidence of major or clinically relevant non-major bleeding events was lower in both dabigatran groups vs. triple therapy [(15.4% vs. 26.9%, p_{ni} <0.001); (20.2% vs 25.7%, p_{ni} <0.001)]. TIMI major bleeding was also lower in dual vs. triple therapy groups. The primary efficacy outcome, incidence of death, MI, stroke, systemic embolism, or unplanned revascularization occurred in 13.7% of both dual therapy groups vs. 13.4% of the triple therapy group (p_{ni} = 0.005). In the sub-group analysis of patients with ACS (52%), ticagrelor was associated with higher bleeding compared to clopidogrel, with and without dabigatran.

These several lines of evidence now suggest that it is safe to treat AF patients who undergo PCI with anticoagulation and clopidogrel monotherapy. Decisions regarding the type of agents used and duration of such therapy should be individualized based on the risk benefit profile of the patient.

The most recent iteration of ESC guidelines provide evidence based recommendations and possible regimens as listed in the **Table 9**.

TABLE 9 RECOMMENDED THERAPEUTIC STRATEGIES FOR PATIENTS NEEDING ANTICOAGULATION AND ANTI PLATELET THERAPY

- Adapted from ESC guideline statement[3]

There is also an emerging interest in evaluation of the efficacy of combination therapy with OAC and single antiplatelet agent in improving clinical outcome. In the recently published ***COMPASS***[89] trial, in patients with stable CAD, addition of rivaroxaban to aspirin lowered major vascular events (4% vs. 6%; HR: 0.74, 95% CI 0.65-0.86, p<0.0001), but increased major bleeding (3% vs.2%; HR 1.66, p<0.0001). There was no significant increase in intracranial bleeding or other critical organ bleeding. There was also a significant net benefit in favor of rivaroxaban plus aspirin and deaths were relatively reduced by 23%. Thus, addition of rivaroxaban to aspirin has the potential to substantially reduce morbidity and mortality from CAD.

In this trial, after a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2.5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). These doses of rivaroxaban are not available in USA for routine use and the data on such combination therapy is still evolving.

9. Conclusions and future directions

The data on the duration of DAPT in patients with CAD continues to evolve especially with the availability of newer stent designs and potent antiplatelet agents and newer oral anticoagulants. Novel DES has been shown to be safer than BMS in terms of device related adverse events with both standard DAPT[90] and S-DAPT[91]. Prolonged DAPT reduces the ischemic events at the cost of bleeding risk, which continues to accrue with longer duration of DAPT. Thus, optimal duration of DAPT remains a moving target. For our readers, we have summarized the future and emerging trials in ***Table10***.

The old adage "there is no free lunch" aptly applies to this clinical dilemma and therefore decisions on DAPT duration require an astute understanding of both the patient's ischemic as well as bleeding risks and "shared decision making" with the patient is recommended.

TABLE 10 COMPARATIVE FEATURES OF PROMINENT FUTURE RANDOMIZED CONTROLLED TRIALS EVALUATING NOVEL DAPT REGIMENS

MI= Myocardial infarction; BARC= Bleeding academic research consortium
GLOBAL LEADERS= A Clinical Study comparing two forms of anti-platelet therapy after stent implantation (NCT01813435); **MASTER DAPT**= Management of high bleeding risk patients post bioresorbable polymer coated stent implantation with an abbreviated versus prolonged DAPT regimen (NCT03023020); **TWILIGHT**= Ticagrelor with Aspirin or alone in high-risk patients after coronary intervention (NCT02270242)

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